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LARYNGEAL CANCER

In order to say that any substance, including cigarette smoke, is a chemical carcinogen in humans, one must demonstrate either

- (1) that the mechanism by which the substance causes the disease is understood, or
- (2) that, in the absence of a such an understanding, all data relevant to the question of whether the substance causes cancer in humans converges in a manner that leaves no plausible alternative hypothesis.

As to the first question, it can be fairly stated that no one understands the mechanism by which a benign cell becomes malignant.<sup>1/</sup> All competent authorities recognize that carcinogenesis is a complex process, involving several factors operating at different points in a sequence.<sup>2/</sup> At the present time, most scientists propose at least a three-step process of initiation, promotion and progression,<sup>3/</sup> and many investigators believe that there are probably five or six different steps, with promotion itself involving several steps.<sup>4/</sup> Furthermore, no one knows in what order these various steps occur,<sup>5/</sup> and none of them is itself well understood.<sup>6/</sup> No one knows how or where tobacco smoke might fit into this process, and no one has ever identified what it might be in smoke which could cause cancer:

Despite a quarter of a century of intensive study in a variety of animal and other

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laboratory systems, it remains unclear which of the many components of cigarette smoke "tar" are the most important causes of human cancer, and so the relative carcinogenicity for humans of tobacco and "tar" of various different compositions cannot be predicted with confidence, nor can it be stated with confidence that everything other than the tar is innocuous.<sup>7/</sup>

As to the second question, there has been no convergence of data suggesting that cigarette smoke has been scientifically proven to be a cause of laryngeal cancer. Those who argue that smoking causes certain diseases, like lung cancer, base their argument primarily on epidemiology. Epidemiology is a statistical science which compares rates of diseases in different populations of people. While statistics show that laryngeal cancer is more common in smokers than in non-smokers, this establishes not causality but only that a statistical association exists between smoking and laryngeal cancer.<sup>8/</sup> Significantly, there is a wide range of other factors, including gender, race, geographic location, occupation, and alcohol consumption, for which similar statistical associations with laryngeal cancer have been found.

Furthermore, although laryngeal cancer has been statistically associated with smoking, rates of larynx cancer have not increased substantially over the last several decades, as have lung cancer rates. If smoking causes laryngeal cancer, and one assumes that cigarette smoking became popular in the 1920's and 1930's, larynx cancer rates should have increased as

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heavy-smoking cohorts grew older in the 1950's, 1960's and 1970's. To the contrary, larynx cancer rates in the United States have lagged behind lung cancer rates, and lung and larynx cancer rates sometimes have demonstrated marked discrepancies.<sup>9/</sup> When anomalous failure of larynx cancer rates to rise over time has been noted in Australia and Great Britain.<sup>10/</sup> Laryngeal cancer rates in Bombay, India, have been among the highest in the world, but lung cancer rates there are rather low. Also, women of the Maori tribe in New Zealand have the highest female rate of lung cancer in the world, but their larynx cancer rate is almost zero.<sup>11/</sup>

In this vein, one of the most vehement critics of cigarette smoking has said:

If I wanted to argue that cigarette smoking was not proved to be the cause of any type of cancer, I would point to the trends in cancer of the larynx in various countries. Although this cancer has been closely related to cigarette smoking in all case-control studies, the trends in incidence and mortality have sometimes been in the opposite direction to the trends for cancer of the lung.<sup>12/</sup>

In England and Wales, at least one study has found that laryngeal cancer mortality has consistently gone down as smoking has gone up, and that the ratio of men to women who have laryngeal cancer has consistently remained about 4:1, despite the increase in recent decades of smoking by women. The authors conclude:

... [U]nlike cancer of the lung, there was no sign of a following trend [i.e. as

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smoking goes up, cancer rates go up] in either mortality rates or male:female ratio which would give sound epidemiological grounds for a causal relationship between cigarette smoking and laryngeal cancer.<sup>13/</sup>

The authors also note that "there is conflicting evidence regarding the role of tobacco smoke in the development of laryngeal cancer." <sup>14/</sup>

In addition, cancer of the larynx is not a very common cancer, even in smokers. The 1982 U.S. Surgeon General's Report notes that there were 11,000 cases of laryngeal cancer, annually in the United States, compared to 130,000 lung cancer cases.<sup>15/</sup>

As noted above, the statistical risk for developing laryngeal cancer has been shown to vary greatly, depending on gender, race, ethnic differences, geography, socioeconomic status, and various other factors:

- (1) There is a marked variation between males and females. Of the 9200 cases reported in the U.S. in 1979, 8100 were in men and 1100 in women. Furthermore, between 1935 and 1970, the incidence of laryngeal cancer in women has shown only a very minimal increase in spite of the fact that lung cancer in women has quadrupled during that same period.<sup>16/</sup> About 2.3% of all malignant tumors in males but only 0.4% of all malignant tumors in females are laryngeal cancers. For males, there are 8.5 cases of laryngeal cancer per 100,000, compared to 1.3 cases per 100,000 for females.<sup>17/</sup>
- (2) There is a marked variation between whites and nonwhites. From 1935 to 1970, cancer of the larynx in the U.S. has increased by 33% in white males, but has increased by 350% in nonwhite men.<sup>18/</sup>

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- (3) There are considerable geographic differences in larynx cancer rates. In parts of India, laryngeal cancer accounts for 7% of all cancers. In Japan, laryngeal cancer constitutes only about 0.7% of all cancer deaths. The incidence of laryngeal cancer is nearly identical in four Scandinavian countries (0.2 per 100,000 in Sweden, Iceland and Norway; 0.3 per 100,000 in Finland). This should be compared to rates for cancer of the lung and bronchus (70.7 per 100,000 in Finland; 13.5, 13.8 and 13.9 per 100,000 for Iceland, Norway and Sweden, respectively).<sup>19/</sup>
- (4) There are differences in the occurrence of laryngeal cancer between urban and rural areas. One study reported that the rate of laryngeal cancer was nearly twice as high in urban areas than in rural areas.<sup>20/</sup>
- (5) As socioeconomic status goes down, laryngeal cancer rates go up.<sup>21/</sup>
- (6) There are ethnic differences in laryngeal cancer rates. Larynx cancer rates are particularly high in areas in which there are large numbers of people of Irish descent. They are also high in areas in which large groups of people of Polish, southern European and British descent live.<sup>22/</sup>
- (7) Many authorities have observed that nutritional deficiencies are strongly associated with cancer of the larynx. For example, studies have shown an elevated risk being associated with deficiencies in vitamin A, vitamin C, iron, and magnesium.<sup>23/</sup>
- (8) In a similar vein, it has been shown that there is an association between poor oral hygiene and laryngeal carcinoma.<sup>24/</sup> A positive association between use of gargles and mouthwashes and laryngeal cancer also has been detected.<sup>25/</sup>

A number of studies show that alcohol is a more significant risk factor for laryngeal cancer than smoking.

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This suggests that the statistical association between smoking and larynx cancer could be due to the confounding effects of alcohol use. Even Doll and Peto, severe critics of smoking, have said:

To say that certain conditions are related to smoking does not necessarily imply that smoking caused (or prevented) them. The relationship may have been secondary in that smoking was associated with some other factor, such as alcohol consumption or a feature of the personality, that caused the disease.<sup>26/</sup>

Tuyns and Audigier conducted a study on subjects in France, and found that cancer of the lung, larynx and esophagus were all elevated in French males who were young adults prior to World War II. During World War II, alcohol availability and consumption were drastically reduced, but tobacco was still readily available. Lung cancer continued its rise in birth cohorts who were young adults during World War II, but both cancer of the larynx and cancer of the esophagus fell in those cohorts who were young adults during World War II. Both of these cancers again continued their rise in cohorts who were young adults after World War II, when alcohol was again more heavily consumed.<sup>27/</sup> This study thus indicates that alcohol is a more significant risk factor for laryngeal cancer than tobacco. McMichael, reviewing death statistics in England and Australia, also suggested that alcohol was more of a risk factor for laryngeal cancer than cigarette smoking.<sup>28/</sup> In 1982, Ramadan, et al., stated:

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"While the traditional role of cigarette smoking as an etiological factor in the development of laryngeal cancer has been brought into question, an increased alcohol consumption has emerged as being clearly associated with an increased risk of laryngeal cancer."<sup>29/</sup>

Several occupations have also been epidemiologically associated with laryngeal cancer. Asbestos workers, brewers and bartenders, machinists, stevedores and dock workers, seamen, and meat cutters all have elevated rates of larynx cancer.<sup>30/</sup> Other occupational settings in which a higher than predicted incidence of laryngeal cancer has occurred are woodworking, nickel refining, metal handling and processing (including grinding), leather-working, farming, textile processing, motor vehicle maintenance work, and mustard gas manufacture.<sup>31/</sup> Laryngeal cancer mortality also tended to be higher in U.S. counties which there were heavy concentrations of chemical and printing industries.<sup>32/</sup>

Some studies have found an excess risk of laryngeal cancer in cement and concrete workers and masons, who would be exposed to dusts in their occupations,<sup>33/</sup> and one study found an elevated risk for persons exposed to "any occupational dust."<sup>34/</sup> In light of the possibility that carcinogenic dusts could become impacted in the larynx, one study has suggested further study of dusty occupations.<sup>35/</sup>

Thus, the epidemiological evidence is so disparate that one could never claim that it converges to the point where one must conclude that smoking causes cancer of the larynx.

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Furthermore, the animal data available on the subject does not strongly support the hypothesis that smoking causes cancer of the larynx. Although some scientists claim larynx cancer can be produced in hamsters, the evidence is problematic:

- (1) The hamster larynx is extraordinarily narrow in comparison with other animal species and humans. Tar deposition data shows that some 1200 times the amount of tar deposits in hamster larynxes than deposits in the hamster lungs when surface area is taken into account.<sup>36/</sup> Thus, the experiment is basically an internal skin painting experiment, i.e., tar is applied directly and continuously to the larynx like tar is applied to mouse skin. Nor surprisingly, tumors result in both places.
- (2) The hamster larynx cancer experiments cannot be uniformly repeated. Some other strains of hamsters have not been shown to get cancer at all, and one group of hamsters exposed to smoke did get cancer, but they lived so much longer than the control hamsters that the researcher could not exclude old age as the cause of the tumors.<sup>37/</sup>

Accordingly, it has not been scientifically established that smoking causes laryngeal cancer.



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FOOTNOTES

- 1/ U.S. Office of Science and Technology Policy, "Chemical Carcinogens, A Review of the Science and Associated Principles, February 1985," Federal Register 50:50 (March 14, 1985) at 10379.
- 2/ 1979 Surgeon General's Report at 45.
- 3/ Weinstein, "The Relevance of Tumor Promotional and Multistage Carcinogenesis to Risk Assessment," Banbury Report 19, Risk Qualification and Regulatory Policy, Cold Spring Harbor Laboratory (1985) at 231.
- 4/ Marx, "Tumor Promoters Carcinogenesis Gets More Complicated," Science 518 (August 11, 1978) at 518.
- 5/ OSHA, "Identification, Classification and Regulations of Potential Occupational Carcinogens," Federal Register 45:15 (January 22, 1980) at 5018.
- 6/ Doll, R., and Peto, R., "The Causes of Cancer" New York: Oxford University Press, (1981) at 1214.
- 7/ Peto and Doll, R., "Passive Smoking," British Journal of Cancer 54 (1986) at 352.
- 8/ 1964 Surgeon General's Report at p. 47.
- 9/ Doll, "Remarks at CIBA Foundation Symposium (110): The Value of Preventive Medicine" (1985) at 140; Doll and Peto, "Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors," British Medical Journal, (1976) at 1533.
- 10/ Austin, D.F., "Larynx," in Shottenfeld and Fraumeni, eds. Cancer: Epidemiology and Prevention (W.B. Saunders, 1982) at pp. 557-58.
- 11/ Id. p. 555.
- 12/ Doll, "Remarks at CIBA Foundation Symposium (110), The Value of Preventive Medicine" (1985) at 140.
- 13/ Ramadan, M.F., et al., "Review: Epidemiology of Laryngeal Cancer," Clin. Otolaryngol 7:417-428 (1982) at 424.
- 14/ Id. p. 425.
- 15/ 1982 Surgeon General's Report at 21, 63.

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- 16/ In DeVita, V.T., et al., eds. Cancer: Principles and Practice of Oncology (Lippicott, 1985) 2nd Ed at 456.
- 17/ "Tumors of the Larynx," in Thawley and Punje, eds. Comprehensive Management of Head and Neck Tumors 1, (W.B. Saunders, 1987) at 870.
- 18/ DeVita, V.T., et al., eds, supra at 456.
- 19/ Austin, supra at 556.
- 20/ Blot, et al., "Patterns of Laryngeal Cancer in the United States," Letter to the Editor, Lancet, (September 1987) (ii) at 674-75.
- 21/ Id.
- 22/ Id.
- 23/ Meyer-Breitung and Burkhardt, Tumors of the Larynx: Histopathology and Clinical Inferences (New York: Springer - Verlag, 1988) at 57-58.
- 24/ Elwood et al, "Alcohol, Smoking, Social and Occupational Factors in the Aetiology of Cancer of the Oral Cavity, Pharynx and Larynx," Int. J. Cancer 34, 603-12 (1984).
- 25/ Zagraniski, supra, at 73.
- 26/ Doll and Peto, "Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors," British  
Med. J. 1 (1976) 1117-1121.
- 27/ Tuyns, A.J., Audigier, J.C., "Double wave cancer increase for Oesophageal and Laryngeal Cancer in France in Relation to Reduced Alcohol Consumption during the Second World War," Digest 14:197-208, (1976).
- 28/ McMichael, A.J., "Increases in Laryngeal Cancer in Britian and Australia in Relation to Alcohol and Tobacco Consumption Trends," Lancet i:1244-1247 (1978).
- 29/ Ramadan, supra at 423.
- 30/ Austin, supra at 559.
- 31/ Zagraniski, et al., "Occupational Risk Factors for Laryngeal Carcinoma: Connecticut, 1975-1980," Am. J. Epidemiology, 124(1) (1986) at 74.
- 32/ Blot, supra at 675.

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- 33/ Zagraniski, supra at 74.
- 34/ Olsen, et al., "Occupational Cases of Laryngeal Cancer," J. Epidemiol. Comm. Health 38: 117-121 (1984).
- 35/ Zagraniski, supra at 74-75.
- 36/ Bernfeld, et al., "Cigarette Smoke Inhalation Studies in Inbred Syrian Golden Hamsters," JNCI 63(3) (1979) at 685, 687.
- 37/ Wehner, A.P., et al., "Increased Lifespan and Decreased Weight in Hamsters Exposed to Cigarette Smoke," Arch. Environ. Health 31:146-153 (1976)